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| 09/987,687 | 11/15/2001 | Matthew C. Coffey | 032775-078 | 7186 |

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| EXAMINER | |
|---|---|
| ANGELL, JON E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/987,687 | COFFEY ET AL. | |
| | Examiner | Art Unit | |
| | J. Eric Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/03 has been entered. The amendment has been entered, and claims 1 and 8-12 have been amended. Claims 1-21 are currently pending in the application.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for delivering a reovirus to a solid tumor to reduce growth of the tumor, wherein said method comprises delivering said reovirus into said solid tumor wherein said solid tumor has an activated Ras pathway;

does not reasonably provide enablement for the full scope encompassed by the claims—such as solid tumors that do not have an activated Ras signaling pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The nature of the invention is virotherapy for tumors

The breadth of the claims

As written, the claims are very broad and encompass the administration of any type of virus which is capable of selectively killing tumor cells to any type of solid tumor.

The unpredictability of the art and the state of the prior art

A review of the prior art indicates that human reovirus require an activated Ras signaling pathway to infect a cancer cell. Specifically, Coffey et al (Science 1998; cited as a reference in the specification) teaches,

> "Human reovirus requires an activate Ras signaling pathway for infection of cultured cells." (See abstract)

Furthermore, Strong et al (EMBO 1998, a reference cited in the specification) also indicates that human reovirus requires an activated Ras signaling pathway for its oncolytic activity. Specifically, Strong teaches:

> "Although the presence or absence of virus receptors on the cell surface remains a major determining factor of the susceptibility of a cell to virus infection, there is now increasing evidence that the intracellular environment plays an important role in dictating the outcome of viral invasion. In the case of the human reovirus, the receptor is the ubiquitous sialic acid, a fact accounting for the observation that the reovirus binds to most mammalian cells. However, neither virus binding nor even internalization assures a productive outcome, suggesting that downstream events are required for reovirus infection. An interesting clue has comes from earlier studies which showed that normal and transformed cells manifested differential sensitivity to reovirus infection. Hashiro et al (1977) reported that certain virally and spontaneously transformed cell lines of murine origin were susceptible to reovirus infection, whereas normal human and subhuman primate cells, primary mouse cells, normal rat kidney cells and baby hamster kidney cells were not." (See p. 3351, paragraph bridging columns 1 and 2); and,
>
> "The usurpation of the Ras signaling pathway therefore constitutes tat basis of reovirus oncolysis." (See abstract).

There does not appear to be any indication in the prior art indicating that any virus other than the reovirus is a capable of selectively killing tumor cells. It is noted that claim 7 specifically includes p-53 expressing viruses, VSV, encephalitis virus, herpes zoster virus, hepatitis virus, influenza virus varicella virus and measles virus. There is no indication in the prior art that these viruses (explicitly claimed in claim 7) are capable of selectively killing tumor cells. Furthermore, one of skill in the art would expect many of these viruses, including

encephalitis virus, herpes zoster virus, hepatitis virus, influenza virus varicella virus and measles virus, to infect normal cells as well as cancer cells, as these viruses are well known to function by infecting non-cancerous cells. Therefore, without evidence to the contrary, it is highly unlikely that these viruses are capable of selectively killing tumor cells without performing additional experimentation.

Working Examples and Guidance in the Specification

The working examples indicate that a human reovirus can be an effective agent for reducing the growth tumors wherein the tumors have an activated Ras signaling pathway (e.g., ras-transformed C3H-10T1/2 tumors). The examples indicate that the reovirus can be effective at inhibiting tumor growth when the reovirus is administered by i.v. injection, i.p. injection and by direct intratumoral injection (which is the most effect, e.g., see Figure 2). There are no examples indicating that the reovirus have an oncolytic effect on non-ras activated tumors. Furthermore, there are no working examples or guidance indicating that a virus other than reovirus (such as the viruses included in claim 7) can be effective at reducing tumor growth when administered by the same routes as the reovirus. Additionally, there are no examples or guidance indicating that any virus other than the reovirus (such as the viruses of claim 7) is capable of selectively killing tumor cells.

Quantity of Experimentation

Since the claims encompass using any virus that can selectively kill tumor cells wherein said virus can be administered to any type of tumor, including ras-activated tumors as well as tumors without activated ras signaling pathway, and considering that the prior art and examples indicate that reovirus has oncolytic activity only in tumor cells with activated Ras signaling

pathway, and considering that there is no evidence presented that viruses such as encephalitis virus, herpes zoster virus, hepatitis virus, influenza virus varicella virus and measles virus are capable of selectively killing tumor cells when it is well known that these viruses infect non-cancer cells; additional experimentation would be required in order to practice the claimed invention to full scope encompassed by the claims. For instance, additional experimentation would be required in order to overcome the art-recognized problem of using an reovirus to inhibit the growth of a tumor without an activated ras pathway; and to determine which other non-reovirus would have a similar effect in Ras-activated and non-ras-activated tumors; and to determine if the viruses other than the reovirus can selectively kill tumor cells.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the unpredictable nature with respect to using reovirus on non-Ras activated tumors, as well as non-reovirus on the encompassed tumors, the limited working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method to the full scope encompassed by the claims is undue.

## *Claim Rejections - 35 USC § 102*

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 7-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334).

Claim 1 has been amended such that claim 1 is now drawn to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor by a base administration of injecting on the same day a composition comprising the virus into multiple sited inside the solid tumor, wherein the volume of the composition injected per site is between about 10% and about 100% of the volume of the tumor.

It is noted that the amended claim does not explicitly indicate that the composition comprising the virus is administered by multiple intratumoral injections, rather the claim is merely drawn to injecting on the same day a composition comprising the virus into multiple sites inside the tumor. As such, the claim encompasses administering the virus composition to multiple sites inside the tumor (on the same day) by injecting the composition into the tumor via a single injection that is not necessarily an intratumoral injection.

The instant rejection is in view of the above-indicated interpretation of claim 1, wherein the injection may be a single injection that results in delivery of the viral composition into multiple sites inside the tumor.

Kooby teaches a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration injecting on the same day a composition comprising the virus into multiple sites

inside the solid tumor, wherein the volume of the composition injected per site is between about 10% and about 100% of the volume of the tumor (meeting the limitations of claim 1).

Kooby teaches that the virus can be a modified herpes simplex virus (HSV) (meeting the limitation of claim 7); that the virus is delivered to one site per 0.25 $cm^3$ of the tumor (meeting the limitation of claim 10), wherein the total volume of the virus composition is at least 30% (meeting the limitations of claim 11), at least 50% (meeting the limitations of claim 12), or wherein the total volume administered is between about 10% to about 100% of the volume of the tumor (meeting the limitations of claim 13).

Specifically, Kooby teaches that multi-mutated HSV type-1 virus (G207) is a replication-competent HSV type-1 (HSV-1) which has demonstrated impressive oncolytic activity in several neurological malignancies, while sparing normal neural tissue (see paragraph bridging p. 1325-1326). Kooby indicates that human colorectal cancer cells were injected into athymic rats and allowed to grow until the tumor volume reached ~50$mm^3$, the tumors were then injected with 50µl of a G207 viral composition (See p. 1327, first full paragraph). It is noted that ~50$mm^3$= ~0.050ml= ~50µl. Therefore, injecting 50µl constitutes injecting about 100% of the volume of the tumor (which is at least 30%, at least 50% and in the range of about 10% to about 100% of the volume of the tumor). Kooby teaches that direct injection of the virus composition suppressed xenograft tumor growth significantly compared to controls (see p. 1328, last full paragraph; and p. 1330, Figure 4). Furthermore, Kooby teaches a single injection of the virus composition to a tumor that has a volume= ~50$mm^3$, thus meeting the limitation of claim 10, wherein the virus is delivered to one site per about 0.25 cubic centimeters of the tumor. It is

noted that $0.25cm^3 = 250mm^3$, thus a tumor with a volume of $50mm^3$ would only require a single injection.

It is noted that claim 1 indicates that the virus is injected such that the virus is injected into multiple sites inside the tumor. Looking to the specification for guidance on the definition of "multiple sites inside the tumor" it is noted that the specification does not explicitly define "multiple sites inside the tumor", but does indicate, "Alternatively, the virus can be delivered to a single site in a large amount of fluid, which enables a wider spread of the virus" (See p. 14, lines 5-10 of the instant specification). Therefore, the claim can be interpreted to encompass a single injection of the virus into a tumor, such that the single injection results in the injection of the viral composition to multiple "sites" (e.g. multiple cells) inside the tumor, wherein the volume of virus injected per site is about 10% to about 100% of the tumor volume. Since the claims encompasses a single injection into the tumor such that the injection results in the injection of the viral composition into multiple sites inside the tumor (e.g., multiple cells inside the tumor), Kooby also teaches by necessity that the single injection would result in the virus being injected into at least 3 and at least 5 sites (e.g., at least 3 and 5 different cells) inside the tumor (thus meeting the limitations of claims 8 and 9).

***Response to Arguments***

7. Applicant's arguments filed 12/23/03 have been fully considered but they are not persuasive.

8. Applicants argue that claim 1 has been amended such that the claim is now drawn to "a base administration of injecting on the same day a composition comprising the virus into multiple sites inside the solid tumor… claims 7 and 10-13 all depend on claim 1, directly or

indirectly, and hence recite all of the elements of claim 1, including the element of multiple injections into a tumor on multiple days." (Emphasis added, see p. 6 of the response).

9. It is respectfully pointed out, as indicated above, the amended claim 1 does not explicitly indicate that the composition comprising the virus is administered by multiple intratumoral injections, rather the claim is merely drawn to a base administration of injecting on the same day a composition comprising the virus into multiple sites inside the tumor. As such, the claim encompasses administering the virus composition to multiple sites inside the tumor (on the same day) by injecting the composition into the tumor via a single injection. Therefore, Kooby does meet all of the limitations of the claims and the rejection is appropriate.

10. It is noted that amending the claim to indicate that the administration comprises multiple intratumoral injections of the viral composition wherein the multiple intratumoral injections are to the same tumor on the same day would obviate this rejection. However, the 103(a) rejection using the combination of the Kooby and Barber reference would still apply, as indicated below.

***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-6 and 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334) in view of Lee et al. (WO 99/08692 filed 12 August 1998 and published on 25 February 1999).

As indicated above, Kooby teaches a method that meets all of the limitations of claim 1, including: a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration injecting on the same day a composition comprising the virus into multiple sites inside the solid tumor, wherein the volume of the composition injected per site is between about 10% and about 100% of the volume of the tumor.

Kooby does not teach that the virus is a reovirus, mammalian reovirus, a human reovirus, a serotype 3 virus, a Dearing strain virus, or that the method further comprises at least one additional administration including (a) delivering the virus by using a transdermal patch, a spray on the skin, or topical administration, wherein the tumor is a superficial tumor; and (b) delivering the virus systemically.

Lee teaches a method for delivering a reovirus serotype 3 Daring strain virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing

tumor cells and wherein the virus is administered in a single dose or in multiple doses (i.e. more than one does) and the multiple doses can be administered concurrently (at the same time) or consecutively (i.e. either before or after the base administration). (See, for instance, abstract; p.3 lines 1-15; p.9, lines 17-20; p.34, lines 9-17; Examples 9 and 10; and Claim 38). Lee also teaches that the reovirus is not known to be associated with disease (see p. 3, lines 15-18), thus making it a safer therapeutic virus than viruses that are known to cause diseases.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Kooby such that the viral vector that is delivered into the tumor is a Dearing strain serotype 3 virus wherein the virus composition that is delivered to each site inside the tumor is between about 10% to about 100% of the volume of the tumor, with a reasonable expectation of success.

One of ordinary skill would have been motivated to substitute the modified HSV-1 virus of Kooby with the Dearing strain 3 reovirus of Lee in order to increase the safety of the method as herpes viruses are known to causes diseases in subjects while reovirus is not known to be associated with any disease.

14. Claims 1, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334) in view Barber et al. (US Patent 5,662,896, published 1997).

It is noted, as indicated above, given the broadest reasonable interpretation of the claims, claim 1 is not necessarily limited to multiple intratumoral injections of the viral composition. In

view of this interpretation, the above rejections are deemed appropriate. However, to the extent that the claims can encompass multiple intratumoral injections of the viral composition, the instant rejection is also deemed appropriate.

As indicated above, Kooby teaches a method that meets all of the limitations of claim 1, including: a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration injecting on the same day a composition comprising the virus into multiple sites inside the solid tumor, wherein the volume of the composition injected per site is between about 10% and about 100% of the volume of the tumor.

Kooby does not explicitly teach that the virus is delivered into multiple sites inside the tumor by multiple intratumoral injections of the viral composition on the same day.

Barber teaches a method for delivering a virus which kills tumor cells (and may be a non-pathogenic, replication competent virus (see col. 10, lines 64-65)) to multiple sites within the mass of the tumor. Specifically, Barber teaches, "Various methods may be utilized within the context of the present invention in order to directly administer the vector construct to the tumor." "For example, within one embodiment a small metastatic lesion may be located and the vector injected several times in several different locations within the body of the tumor" (emphasis added, see col. 11, lines 5-8), thus indicating administration of at least 3 injections (because "several" indicates "greater than two but less than many", as defined in Merriam-Webster's Collegiate Dictionary, Tenth Edition, pg. 1073 as mentioned in the previous Office Action).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the method of Kooby such that the method comprised delivering the virus to several different sites (such as at least 3, at least 5, or more sites) inside the tumor mass in order to effectively treat the tumor. The exact number of times would be a matter of routine experimentation in order to determine the most effective number of sites to deliver the virus.

One of ordinary skill would have been motivated to combine the references in order to more effectively treat the tumor because Barber teaches a method comprising administering a replication competent virus to several different sites inside a tumor in order to treat the tumor. Specifically, Barber teaches a working example wherein multiple injections of the virus are given to the tumor every two to three days (see col. 37, lines 44-45), thus indicating administering multiple injections on day zero and then more multiple injections on either day 2 or day 3 in order to treat a tumor in a subject.

15. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 99/08692) in view of Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334).

It is noted, as indicated above, given the broadest reasonable interpretation of the claims, claim 1 is not necessarily limited to multiple intratumoral injections of the viral composition. However, to the extent that the claims can encompass multiple intratumoral injections of the viral composition, the instant rejection is deemed appropriate.

Lee teaches a method for directly delivering an oncolytic reovirus serotype 3 Daring strain virus (which is a human serotype 3 reovirus) by injection into a solid tumor to reduce growth of the tumor. Lee teaches that the method comprises administering an effective amount

of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells and wherein the virus is administered in a single dose or in multiple doses (i.e. more than one does) and the multiple doses can be administered concurrently (at the same time) or consecutively (i.e. either before or after the base administration). (See, for instance, abstract; p.3 lines 1-15; p.9, lines 17-20; p.34, lines 9-17; Examples 9 and 10; and Claim 38). Therefore, Lee teaches a method of injecting a reovirus into a solid tumor (e.g., see claim 27) comprising multiple doses (i.e., multiple injections) which are administered concurrently (i.e., on the same day). Lee teaches that the method can comprise the additional administration of the therapeutic virus by other routes of administration, including systemic administration of human reovirus; or topically or by spray (e.g., see page 9). It is noted that multiple administrations encompasses more than one administration.

Lee does not teach that the volume of the viral composition that is injected into the tumor is about 10% to about 100% of the total volume of the tumor, nor does Lee teach that the oncolytic virus that is administered is a modified HSV.

Kooby teaches a method for reducing the growth of a tumor by injecting into a solid tumor a viral composition comprising an oncolytic modified HSV wherein the volume of the viral composition that is administered is between about 10% and about 100% of the tumor volume. Specifically, Kooby teaches that multi-mutated HSV type-1 virus (G207) is a replication-competent HSV type-1 (HSV-1) which has demonstrated impressive oncolytic activity in several neurological malignancies, while sparing normal neural tissue (see paragraph bridging p. 1325-1326). Kooby indicates that human colorectal cancer cells were injected into athymic rats and allowed to grow until the tumor volume reached ~50mm$^3$, the tumors were then

injected with 50µl of a G207 viral composition (See p. 1327, first full paragraph). It is noted that ~50mm$^3$= ~0.050ml= ~50µl. Therefore, injecting 50µl constitutes injecting about 100% of the volume of the tumor (which is at least 30%, at least 50% and in the range of about 10% to about 100% of the volume of the tumor). Kooby teaches that direct injection of the virus composition suppressed xenograft tumor growth significantly compared to controls (see p. 1328, last full paragraph; and p. 1330, Figure 4).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Lee, such that the number of injections on the same day were at least 3 or at least 5 injections, wherein the volume of the viral composition that is delivered is between about 10%-100% of the tumor volume (for claim 1), and to modify the method of Lee such that the oncolytic virus that is delivered is a modified HSV (as taught by Kooby); with a reasonable expectation of success.

The motivation to modify the method of Lee such that the injected a volume of viral composition that is between 10% and about 100% of the total tumor volume and to use an oncolytic modified HSV, because Kooby teaches that an effective dose of composition comprising an oncolytic virus (specifically a modified HSV) is between 10% and about 100% of the total tumor volume, and one would have been motivated to adjust the number of injections on the same day such that at least 3 or at least 5 injections of the oncolytic virus, because Lee teaches that effective treatment depends on several factors including the amount of virus administered, the type and size of the tumors and indicates that multiple doses may be required (see p. 9, lines 7-20), thus making the number of injections a matter of routine optimization.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Eric Angell
Art unit 1635